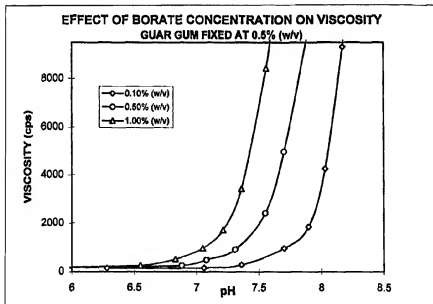




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(54) Title: OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE



(57) Abstract

The present invention is directed to ophthalmic compositions containing a gelling amount of a combination of galactomannan polysaccharides and borates. The compositions gel or partially gel upon administration to the eye. The present invention also discloses methods of topical ophthalmic administration of the compositions of the eye.

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OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE

Background of the Invention

The present invention relates to the use of adjuvants in topical ophthalmic compositions. In particular, the present invention relates to pharmaceutical compositions comprising galactomannan polymers in combination with borates, and methods for the controlled administration of pharmaceutically active agents to patients, wherein the compositions are administered as liquids which thicken to form gels upon instillation into the eye. The transition from liquid to gel is primarily due to the change in pH and ionic strength.

Topical ophthalmic compositions have taken the form of liquids, ointments, gels and inserts. Liquid compositions for drop-wise instillation of pharmaceutically active agents to the eye provide for easy administration, but they do not always provide for an accurate dosage amount, as portions of the liquid are often blinked away during administration or drained down the punctum into the nasal passage. Ointments and gels, which usually reside in the eye longer than a liquid and therefore provide for more accurate administration, often interfere with a patient's vision. Ocular inserts, both bioerodible and non-bioerodible, are also available and allow for less frequent administration of drug. These inserts, however, require complex and detailed preparation and are frequently uncomfortable to the wearer. An additional problem with non-bioerodible inserts is that they must be removed after use.

U.S. Patents Nos. 4,136,173 (Pramoda, et al.) and 4,136,177 (Lin, et al.) disclose the use of therapeutic compositions containing xanthan gum and locust bean gum which are administered in liquid form and gel upon instillation. These disclosures describe a mechanism for transition from liquid to gel involving pH change. pH sensitive gels such as carbomers, xanthan, gellan, and those described above, need to be formulated at or below the pKa of their acidic groups (typically at a pH of about 2 to 5). Compositions formulated at low pH, however, are irritating to the eye. U.S. Patent No. 4,861,760 (Mazuel, et al.) discloses ophthalmic compositions containing gellan gum which are administered to the eye as non-gelled liquids and gel upon instillation due to a change in ionic strength. These systems do not involve the use of small cross-linking molecules, but instead provide gel characteristics due to self cross-linking during ionic condition changes. Gels involving the cross-linking of polysaccharides with borates are disclosed for use as well fracturing fluids in U.S. Patent Nos. 5,082,579, 5,144,590, and 5,160,643. These patents describe the use of borates and polysaccharides for industrial oil well excavation.

The ophthalmic use of current gelling liquid systems have a number of drawbacks. For example, natural polymers such as xanthan gum have the disadvantage of lot to lot variability due to variations in source and/or limited manufacturing controls during processing. These variabilities cause significant undesirable changes in the properties of the compound, such as variable gelling characteristics. Thermogelling systems such as polyethylene oxide/ polypropylene oxide block copolymers ("PEO/PPO") lose water in order to form gels, and consequently result in turbid gels. Polyvinyl alcohol ("PVA")-borate combination gelling systems need to be formulated at low pH, and therefore, can cause ocular irritation upon instillation. Other gelling systems have viscosity, rehydration and cloud point instability problems associated with autoclaving.

Polyvinyl alcohol crosslinking with borates have been disclosed in U.S. Patent No. 4,255,415 (Sukhbir et al.). These compositions are pre-formed gels, and are therefore hard to dispense. WIPO Publication No. WO 94/10976 (Goldenberg et al.) discloses a low pH PVA-borate delivery system that does go through liquid/gel transition. This system has the disadvantage, however, of limited gelling effects, and only at certain concentrations of PVA depending on the molecular weight of the PVA utilized. Furthermore, since the crosslinking sites are unlimited with this system, strong local gelation upon addition of base has limited its manufacturing, and therefore, polyvinyl pyrrolidone presumably has been included in these compositions to overcome the shortcoming. The novel gelling system of the present invention does not have the above limitation.

Summary of the Invention

The present invention is directed to topical ophthalmic compositions comprising galactomannan polymers and borate compounds which provide controlled administration of a drug to the eye. The invention is based on a new gelling system which comprises a galactomannan polysaccharide and a borate crosslinker which forms a gel upon increases in pH and ionic strength. In this novel system, bisdiol borates crosslink with the cis diol groups of the sugar moieties of the polysaccharide. The compositions are administered as liquids or partially gelled liquids (hereinafter "liquids") which thicken to form gels upon instillation into the eye. Alternatively, the compositions may not contain a pharmaceutically active agent, and can be administered to the eye for lubrication or to supplement tears in the treatment of, for example, dry eye.

The present invention galactomannan-borate gelling system has several advantages over other gelling systems. One advantage is that the compositions of the present invention are clear solutions and the resultant gel is also crystal clear. While other systems may become opaque or cloudy upon instillation, the crystal clear gel of the present invention provides greater clarity of vision to the treated eye. The present invention compositions may be formulated at slightly acidic to neutral pH and require only a minor pH change to activate gelation (i.e., about 0.5 to 1.0 pH unit). This feature minimizes possible irritation of the eye resulting from acidic exposure, such as may result with other pH sensitive systems which require a pH change of about 2.4 to about 4.4 pH units (i.e., are formulated with a pH of about 3-5). Galactomannan polymers are also heat stable and show no cloud point even during autoclaving conditions. As such, viscosity and rehydration problems resulting from batch scale up, such as exist with PVA and carbomer polymer systems, are not present with the galactomannan polymer containing compositions of the present invention.

Galactomannan polysaccharides are non-ionic and, in combination with borates at acidic to neutral pH, are also essentially non-ionic. Thus, the polymer system is completely compatible with anionic, neutral and cationic drugs. Furthermore, the preservative efficacy of the preservatives are not compromised by the presence of the polymer. Typically, the efficacy of benzalkonium chloride or other cationic preservatives are compromised with anionic polymers such as gellan and carageenan, and excess preservative may therefore be needed in those systems. Increases in preservative concentration may also increase irritation and toxicity of the composition.

The galactomannan-borate gelling system of the present invention has other advantages. Galactomannan polymers have a relatively low molecular weight and are therefore easy to manufacture and scale up. Galactomannan polymers are also readily available and have

been used in food and personal care products such that the polymers are considered to be safe. Furthermore, control or manipulation of the gelling characteristics of the galactomannan-borate gelling compositions of the present invention is relatively simple as compared with prior art systems. The gelling properties of other single polymer systems, such as ionomers, e.g., gellan and carageenans, and thermogels, e.g., poloxamines and poloxamers, are typically related to the molecular weight and the number of functional groups of the polymers. Thus, in order to change the gel point or degree of gelation of those prior art systems, one would need to modify the base polymer - a labor intensive activity. In contrast, by simply manipulating the borate to galactomannan ratio in the present invention compositions, a wide range of gelling characteristics is available in order to fine tune the compositions to the targeted requirements (see FIGS. 1 and 2). Moreover, as illustrated in FIG. 3, the galactomannans of the present invention (e.g., guar gum) demonstrate excellent gelling consistency and reproducibility, though the type or source of the galactomannan is varied.

Still other advantages are present in the compositions of the present invention. The galactomannan polymer and the borate crosslinker compositions of the present invention are liquids and, therefore, easy to dispense. Some gelling systems such as gellan gum, as disclosed in U.S. Patent No. 4,861,760 (Mazuel et al.), are thixotropic, which may require shaking to increase the fluidity and ease of dispensing. The present invention compositions contain a relatively low concentration of galactomannan (about 0.2 to 0.5%) as compared to some thermogelling systems such as PEO/PPO block copolymers, which require very high concentrations. Lower concentrations of the gelling polymer provide lower potential toxicity and ease of preservation from microbial contamination over higher concentration systems.

The methods of the present invention involve the topical administration of the galactomannan-borate containing compositions of the present invention.

The present invention is also directed to methods of sterilization of the galactomannans involving autoclaving.

Brief Description of the Drawings

FIG. 1 is a graph illustrating the gelling characteristics of various concentrations of guar gum in the presence of borate, relative to pH.

FIG. 2 is a graph illustrating the gelling characteristics of various concentrations of borate in the presence of guar gum, relative to pH.

FIG. 3 is a graph illustrating the uniformity of the gelling characteristics of three different types/sources of guar gum.

Detailed Description of the Invention

The present invention is directed to ophthalmic compositions which comprise one or more galactomannan polysaccharide(s) and one or more borate compound(s). The present invention is also directed to methods of using these compositions to treat various ophthalmic disorders including dry eye, glaucoma, ocular hypertension, infection, allergy and inflammation.

The types of galactomannans that may be used in the present invention are typically derived from guar gum, locust bean gum and tara gum. As used herein, the term

“galactomannan” refers to polysaccharides derived from the above natural gums or similar natural or synthetic gums containing mannose or galactose moieties, or both groups, as the main structural components. Preferred galactomannans of the present invention are made up of linear chains of (1-4)- β -D-mannopyranosyl units with α -D-galactopyranosyl units attached by (1-6) linkages. With the preferred galactomannans, the ratio of D-galactose to D-mannose varies, but generally will be from about 1:2 to 1:4. Galactomannans having a D-galactose:D-mannose ratio of about 1:2 are most preferred. Additionally, other chemically modified variations of the polysaccharides are also included in the “galactomannan” definition. For example, hydroxyethyl, hydroxypropyl and carboxymethylhydroxypropyl substitutions may be made to the galactomannans of the present invention. Non-ionic variations to the galactomannans, such as those containing alkoxy and alkyl (C1-C6) groups are particularly preferred when a soft gel is desired (e.g., hydroxypropyl substitutions). Substitutions in the non-cis hydroxyl positions are most preferred. An example of non-ionic substitution of a galactomannan of the present invention is hydroxypropyl guar, with a molar substitution of about 0.4. Anionic substitutions may also be made to the galactomannans. Anionic substitution is particularly preferred when strongly responsive gels are desired.

The borate compounds which may be used in the compositions of the present invention are boric acid and other pharmaceutically acceptable salts such as sodium borate (borax) and potassium borate. As used herein, the term “borate” refers to all pharmaceutically suitable forms of borates. Borates are common excipients in ophthalmic formulations due to good buffering capacity at physiological pH and well known safety and compatibility with a wide range of drugs and preservatives. Borates also have inherent bacteriostatic and fungistatic properties, and therefore aid in the preservation of the compositions.

The present invention compositions comprise one or more galactomannan(s) in the amount of from about 0.1 to 5% weight/volume ("w/v") and borate in the amount of from about 0.05 to 5% (w/v). Preferably, the compositions will contain 0.2 to 2.0% (w/v) of galactomannan and 0.1 to 2.0% (w/v) of a borate compound. Most preferably, the compositions will contain 0.3 to 0.8% (w/v) of galactomannan and 0.25 to 1.0% (w/v) of a borate compound. The particular amounts will vary, depending on the particular gelling properties desired. In general, the borate or galactomannan concentration may be manipulated in order to arrive at the appropriate viscosity of the composition upon gel activation (i.e., after administration). As shown in FIGS. 1 and 2, manipulating either the borate or galactomannan concentration provides stronger or weaker gelation at a given pH. If a strongly gelling composition is desired, then the borate or galactomannan concentration may be increased. If a weaker gelling composition is desired, such as a partially gelling composition, then the borate or galactomannan concentration may be reduced. Other factors may influence the gelling features of the compositions of the present invention, such as the nature and concentration of additional ingredients in the compositions, such as salts, preservatives, chelating agents and so on. Generally, preferred non-gelled compositions of the present invention, i.e., compositions not yet gel-activated by the eye, will have a viscosity of from about 5 to 1000 cps. Generally, preferred gelled compositions of the present invention, i.e., compositions gel-activated by the eye, will have a viscosity of from about 50 to 50,000 cps.

The galactomannans of the present invention may be obtained from numerous sources. Such sources include guar gum, locust bean gum and tara gum, as further described below. Additionally, the galactomannans may also be obtained by classical synthetic routes or may be obtained by chemical modification of naturally occurring galactomannans.

Guar gum is the ground endosperm of *Cyamopsis tetragonolobus* (L.) Taub. The water soluble fraction (85%) is called "guaran" (molecular weight of 220,000), which consists of linear chains of (1-4)- β -D mannopyranosyl units with α -D-galactopyranosyl units attached by (1-6) linkages. The ratio of D-galactose to D-mannose in guaran is about 1:2. The gum has been cultivated in Asia for centuries and is primarily used in food and personal care products for its thickening property. It has five to eight times the thickening power of starch. Its derivatives, such as those containing hydroxypropyl or hydroxypropyltrimonium chloride substitutions, have been commercially available for over a decade. Guar gum may be obtained, for example, from Rhone-Polulenc (Cranbury, New Jersey), Hercules, Inc. (Wilmington, Delaware) and TIC Gum, Inc. (Belcamp, Maryland).

Locust bean gum or carob bean gum is the refined endosperm of the seed of the carob tree, *ceratonia siliqua*. The ratio of galactose to mannose for this type of gum is about 1:4. Cultivation of the carob tree is old and well known in the art. This type of gum is commercially available and may be obtained from TIC Gum, Inc. (Bekamp, Maryland) and Rhone-Polulenc (Cranbury, New Jersey).

Tara gum is derived from the refined seed gum of the tara tree. The ratio of galactose to mannose is about 1:3. Tara gum is not produced in the United States commercially, but the gum may be obtained from various sources outside the United States.

In order to limit the extent of cross-linking to provide a softer gel characteristic, chemically modified galactomannans such as hydroxypropyl guar may be utilized. Modified galactomannans of various degree of substitution are commercially available from Rhone-Poulenc (Cranbury, New Jersey). Hydroxypropyl guar with low molar substitution (e.g., less than 0.6) is particularly preferred.

Other ingredients may be added to the compositions of the present invention. Such ingredients generally include tonicity adjusting agents, chelating agents, active pharmaceutical agent(s), solubilizers, preservatives, pH adjusting agents and carriers. Other polymer or monomeric agents such as polyethylene glycol and glycerol may also be added for special processing. Tonicity agents useful in the compositions of the present invention may include salts such as sodium chloride, potassium chloride and calcium chloride; non-ionic tonicity agents may include propylene glycol and glycerol; chelating agents may include EDTA and its salts; solubilizing agents may include Cremophor EL® and tween 80; other carriers may include amberlite® IRP-69; pH adjusting agents may include hydrochloric acid, Tris, triethanolamine and sodium hydroxide; and suitable preservatives may include benzalkonium chloride, polyquaternium-1 and polyhexamethylene biguanide. The above listing of examples is given for illustrative purposes and is not intended to be exhaustive. Examples of other agents useful for the foregoing purposes are well known in ophthalmic formulation and are contemplated by the present invention.

Combination of the gelling system of the present invention with prior art gelling systems is also contemplated by the present invention. Such systems may include the inclusion of ionomers, such as xanthan, gellan, carageenan and carbomers, and thermogels, such as ethylhydroxyethyl cellulose.

In general, the compositions of the present invention will be used to administer various pharmaceutically active compounds to the eye. Such pharmaceuticals may include, but are not limited to, anti-hypertensive, anti-glaucoma, neuro-protective, anti-allergy, mucosecretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

Examples of pharmaceutically active agents which may be included in the compositions of the present invention, and administered via the methods of the present invention include,

but are not limited to: glaucoma agents, such as betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors and prostaglandins; dopaminergic antagonists; post-surgical antihypertensive agents, such as para-amino clonidine (apraclonidine); anti-infectives, such as ciprofloxacin and tobramycin; non-steroidal and steroidal anti-inflammatories, such as naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol and dexamethasone; proteins; growth factors, such as epidermal growth factor; and anti-allergics.

Optionally, the compositions of the present invention may be formulated without a pharmaceutically active compound. Such compositions may be used to lubricate the eye or provide artificial tear solutions to treat, for example, dry eye. In general, artificial tear solutions will contain tonicity agents, polymers and preservatives, as described above. The amount of galactomannan and borate contained in the artificial tear solutions will vary, as described above, but will generally be in the amount of from 0.1 to 3.0% (w/v) and 0.1 to 2.0 % (w/v), respectively.

In general, the compositions of the present invention are formulated in two parts. The galactomannan polymer is hydrated and sterilized (Part I). Any pharmaceutical agent(s) and/or other ingredients to be included in the composition are then dissolved in water and sterile filtered (Part II). Parts I and II are then combined and the pH of the resultant mixture is adjusted to the target level, generally 6.0 to 7.0. If the pharmaceutical agent(s) to be included have low water solubility, they will generally be added last. In certain cases, it may be preferred to sterilize the pharmaceutical agent(s) separately, and then aseptically add the agent(s) and other ingredients together.

Sterilization of the galactomannan polysaccharide can be accomplished by autoclaving. Since the polymers undergo depolymerization at the extreme conditions of autoclaving, non-aqueous autoclaving is generally preferred. This can be accomplished by dispersing the

polymer in a suitable organic liquid such as low molecular weight polyethylene glycols. The resulting suspension may then be autoclaved to sterilize the polymer. The sterilized polymer is then hydrated aseptically, prior to admixture with the other ingredients.

The following example illustrates a novel method of sterilizing a galactomannan polysaccharide of the present invention:

Example 1

Preliminarily, a compounding vessel (20 L stainless steel pressure can), a 0.2 micron sterilizing filter, a receiving vessel (20 L carboy), a 4.5 micron polishing filter, a 0.2 micron sterilizing filter, a vent filter, and the filling equipment are sterilized by autoclaving.

In a beaker equipped with an overhead agitator, add the weighed amount of polyethylene glycol 400 (200g). While mixing slowly disperse the weighed amount of hydroxypropyl ("HP")Guar gum (100g). Mix until completely homogeneous. In a 500 ml Schott bottle, equipped with a magnetic stir bar, weigh exactly 120.0g of the HPGuar gum/PEG-400 dispersion. Prepare to sterilize by autoclaving. In a second identical 500 ml Schott bottle weigh exactly 120.0g of the same dispersion. Prepare to use as a dummy during the autoclaving cycle. To both bottles add 1.3 ml of purified water (amount equivalent, by volume, of the microorganism suspension used to inoculate the bottles during the validation study). Mix both bottles for 10 minutes using a magnetic stir plate. Autoclave the HPGuar gum/PEG-400 dispersion using the validated time-temperature cycle of 80 minutes at 125°C.

The other set of ingredients to be included in the final formulation may be prepared separately by various methods known in the art. The resultant mixture can be added by

sterile filtration to the compounding vessel, along with the HPGuar gum/PEG-400 preparation.

Aseptically transfer the sterilized HPGuar gum/PEG-400 dispersion into the pre-sterilized compounding vessel. Rinse the bottle content with sterilized purified water. Bring the content of the compounding vessel to exactly 95% of the theoretical batch weight (19.0 liters or 19.06 Kg) using sterile room temperature purified water. Allow the HPGuar gum/PEG slurry to hydrate while mixing, at moderate speed, in the compounding vessel for a minimum of 2 hours. Transfer the contents of the compounding vessel through a 4.5 micron pre-sterilized polishing filter into the pre-sterilized receiving vessel equipped with a stir bar. There will be some loss of the contents due to the product held in filter housing and filter cartridge. (If a pressure can is used as compounding vessel, the recommended pressure for clarification filtration is approximately 30 psi.) Check and adjust pH, if necessary, to 6.9-7.1 (target 7.0) using 1N NaOH or 1N HCl. Approximately 3-4 ml of 1N NaOH per 1 liter of final batch weight is needed to achieve the desired pH. QS to final batch weight using sterile purified water. Mix at low speed for a minimum of 30 minutes.

The following examples further illustrate preferred ophthalmic compositions of the present invention:

Example 2

The following is an example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.68*
Boric Acid	0.5
Guar Gum	0.5
PEG-400	1.0
Sodium Chloride	0.5
Benzalkonium Chloride	0.01
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.5
Purified Water	QS

* 0.68% Timolol Maleate is equivalent to 0.5% Timolol.

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The above formulation is prepared by first preparing a Part I and Part II mixture. The guar gum is first dispersed in PEG-400 and autoclaved as Part I. The other ingredients are dissolved in about 90% of the volume of water and sterile filtered in a receiving vessel as Part II. Part I is then added to Part II aseptically. The pH may then be adjusted aseptically and the batch is then brought to final weight (volume). The combined solution is then passed through a 1.0 μ m polish filter, aseptically, to remove the particulates.

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Example 3

The following is another example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.34*
Boric Acid	0.5
Guar Gum	0.25
Glycerol	1.0
Benzalkonium Chloride	0.005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 7.0
Purified Water	QS

* 0.34% Timolol Maleate is equivalent to 0.25% Timolol.

The above composition may be prepared in a similar way as the Example 2 composition.

Example 4

The following is an example of an artificial tear solution.

Compound	Amount % (w/v)
Boric Acid	0.5
Hydroxypropyl Guar	0.3
Propylene glycol	1.4
Polyquaternium-1	0.0005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.8
Purified Water	QS

The above composition may be prepared in a similar way as the Example 2 composition.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. A topical ophthalmic composition comprising one or more galactomannan(s) and one or more borate compound(s), wherein the galactomannan and the borate compound are contained in the composition in concentrations effective to create a gel or partial gel when the composition is administered to an eye.

2. A composition of claim 1, wherein the concentration of the galactomannan is about 0.1 to 5% (w/v) and the concentration of the borate compound is about 0.05 to 5.0% (w/v).

3. A composition of claim 1, wherein the galactomannan is selected from the group consisting of guar gum, locust bean gum, tara gum and chemically modified derivatives thereof.

4. A composition of claim 1, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

5. A composition of claim 1, wherein the galactomannan is hydroxypropyl guar and the borate compound is boric acid.

6. A composition of claim 1, wherein the galactomannan is guar gum and the borate compound is boric acid.

7. A composition of claim 5, wherein the composition comprises hydroxypropyl guar in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

8. A composition of claim 6, wherein the composition comprises guar gum in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

9. A composition of claim 1, further comprising one or more pharmaceutically active agent(s).

10. A composition of claim 9, wherein the concentration of the galactomannan is about 0.1 to 5% (w/v) and the concentration of the borate compound is about 0.05 to 5.0% (w/v).

11. A composition of claim 9, wherein the pharmaceutically active agent(s) is/are selected from the group consisting of: anti-hypertensive, anti-glaucoma, neuro-protective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

12. A composition of claim 9, wherein the pharmaceutically active agent is selected from the group consisting of: betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors, prostaglandins; post-surgical antihypertensive agents, apraclonidine; ciprofloxacin, tobramycin; naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol, dexamethasone; proteins and growth factors.

13. A method of delivering a pharmaceutical agent to the eye which comprises topically administering to the eye a composition comprising one or more pharmaceutically active agent(s), one or more galactomannan(s) and one or more borate compound(s), wherein the galactomannan and the borate compound are contained in the composition in concentrations effective to create a gel or partial gel when the composition is administered to the eye.

14. A method of claim 13, wherein the composition comprises the galactomannan in a concentration of about 0.1 to 5% (w/v) and the borate compound in a concentration of about 0.05 to 5% (w/v).

15. A method of claim 13, wherein the galactomannan is selected from the group consisting of guar gum, locust bean gum, tara gum and chemically modified derivatives thereof.

16. A method of claim 13, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

17. A method of claim 13, wherein the galactomannan is hydroxypropyl guar and the borate compound is boric acid.

18. A method of claim 13, wherein the galactomannan is guar gum and the borate compound is boric acid.

19. A method of claim 17, wherein the composition comprises hydroxypropyl guar in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

20. A method of claim 18, wherein the composition comprises guar gum in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

21. A composition of claim 13, wherein the pharmaceutically active agent(s) is/are selected from the group consisting of: anti-hypertensive, anti-glaucoma, neuro-protective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

22. A composition of claim 13, wherein the pharmaceutically active agent is selected from the group consisting of: betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors, prostaglandins; post-surgical antihypertensive agents, apraclonidine; ciprofloxacin, tobramycin; naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol, dexamethasone; proteins and growth factors.

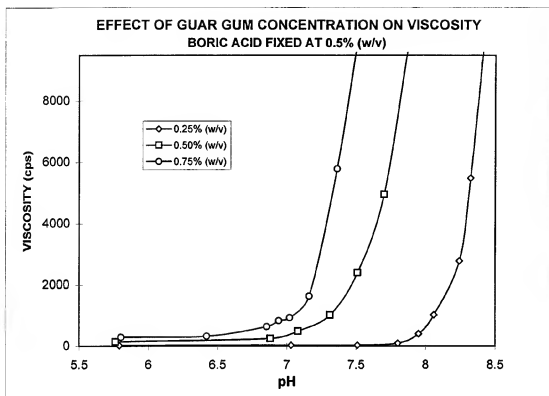


FIG. 1

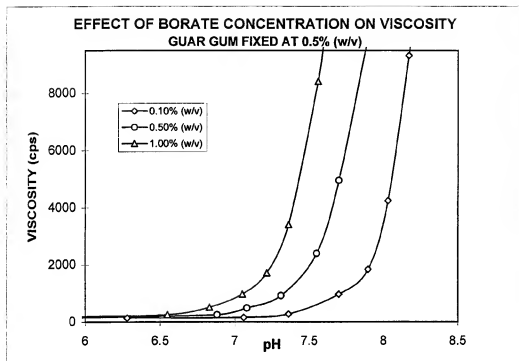


FIG. 2

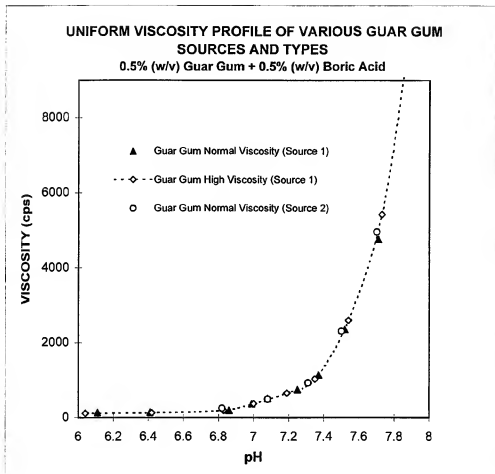


FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/14596

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K47/36 A61K47/02

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category * Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

X US 4 136 178 A (LIN SONG-LING ET AL)
23 January 19791-4, 6,
8-16, 18,
20-22see the whole document
---A US 4 136 177 A (LIN SONG-LING ET AL)
23 January 1979
cited in the application
---A US 5 160 643 A (DAWSON JEFFREY C)
3 November 1992
cited in the application
---A US 4 861 760 A (MAZUEL CLAUDE ET AL)
29 August 1989
cited in the application

-/--

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

2 November 1998

Date of mailing of the international search report

10/11/1998

Name and mailing address of the ISA
European Patent Office, P.O. Box 5818 Patentlaan 2
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Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fischer, W

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/US 98/14596

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 082 579 A (DAWSON JEFFREY C) 21 January 1992 cited in the application -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/14596

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 13-20
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter: Int'l Application No

PCT/US 98/14596

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